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Scientific and Technical Information Center
SEARCH REQUEST FORM

TECH/CHEM. DIVISION

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Date: 3/3/2001 Requester's Full Name: Sabahastin S. J. Examiner #: 74144
Art Unit: 1616 Phone (305) 3910 Serial Number: 09/971,960

Results Format Preferred (circle): PAPER DISK E-MAIL

To ensure an efficient and quality search, please attach a copy of the cover sheet, claims, and abstract or fill out the following:

Title of Invention: 5-membered Heterocycles as inhibitors of Leucocyte adhesion as VLA antagonists

Inventors (please provide full names): Ulrich Stitz et al

Earliest Priority Date: 11/15/96 (German Priority 196-47-380.2)

Search Topic:

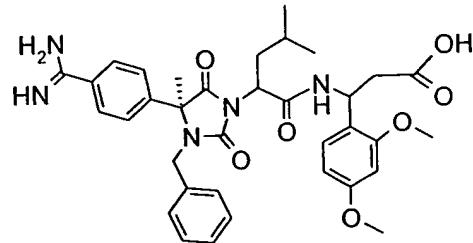
Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc., if known.

*For Sequence Searches Only: Please include all pertinent information (parent, grandchild, divisional, or issued patent numbers) along with the appropriate serial number.

Please search the compounds of formula (1), claims 1
Preparation of suppressing inflammation and
for a method of
antagonising VLA-4. * (No Heterocycle)

Example 53:

(R,S)-3-((R,S)-2-((S)-4-(4-(Amino-imino-methyl)phenyl)-3-benzyl-4-methyl-2,5-dioxoimidazolin-1-yl)-2-(2-methylpropyl)acetyl amino)-3-(2,4-dimethoxyphenyl)propionic acid



Elected Species

No Hetero to L-2
Searched

Please see attached cl 21+22

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Searcher: STIN D
Searcher Phone #: _____
Searcher Location: _____
Data Searcher Picked Up: 3
Date Completed: 3-13
Searcher Prep & Review Time: 20
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Type of Search
NA Sequence (#)
AA Sequence (#)
Structure (#)
Bibliographic
Litigation
Fulltext
Other

Vendors and Cost
 STN 000 Dialog
 Questel/Orbit Dr. Link
 Lexis/Nexis Westlaw
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Dear Examiner,
You can help us in our efforts to get searches back to you in a timely manner by including your art unit and room number on all searches you submit to the STIC.
Thanks from the STIC-Biotech/Chemistry Library

WJD
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BOX AF - EXPEDITED HANDLING

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No. 026083/0138

In re patent application of

Group Art Unit: 1616

Hans Ulrich Stilz et al.

Serial No. 08/971,960

Examiner: S. Qazi

Filed: November 17, 1997

For: 5-MEMBERED RING HETEROCYCLES AS INHIBITORS OF LEUCOCYTE
ADHESION AND AS VLA-4 ANTAGONISTS

AMENDMENT AND REQUEST FOR RECONSIDERATION UNDER 37 C.F.R. § 1.116

Assistant Commissioner for Patents
Washington, D.C. 20231
BOX AF

Sir:

In response to the outstanding Office Action mailed May 14, 1999, please amend the above-identified application as follows:

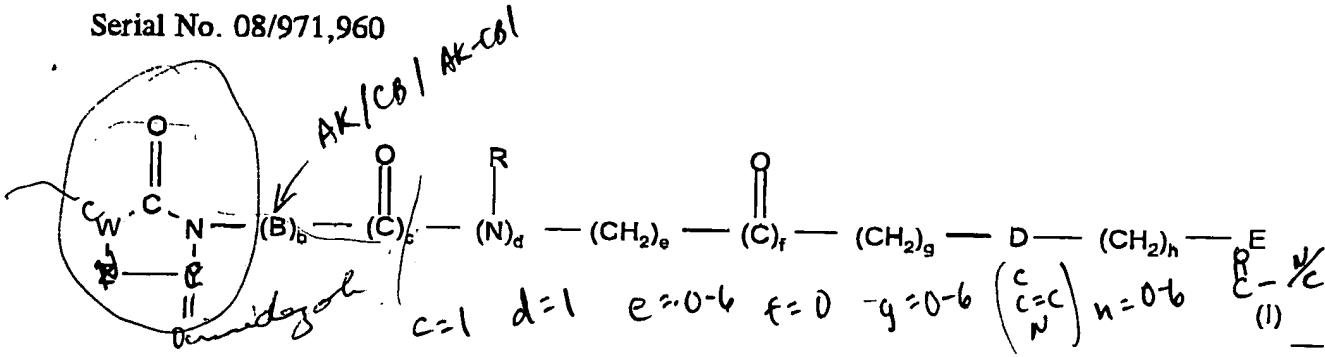
IN THE CLAIMS:

Please cancel claims 1-20 and 25-38 without prejudice or disclaimer. Applicants reserve the right to file one or more continuing applications directed to their subject matter.

Please rewrite the following claims:

21. (amended) A method for suppressing inflammation comprising administering to a subject in need thereof an effective amount of [the preparation as claimed in claim 1] a preparation comprising an effective amount of at least one compound of the formula I:

Serial No. 08/971,960

in whichW is $R^1-A-C(R^{13})$;Y is a carbonyl;Z is $N(R^0)$;

A is a bivalent radical from the group consisting of (C_1-C_6) -alkylene, (C_2-C_7) -cycloalkylene, phenylene, phenylene- (C_1-C_6) -alkyl, (C_1-C_6) -alkylenephenoxy, phenylene- (C_2-C_6) -alkenyl or a bivalent radical of a 5- or 6-membered saturated or unsaturated ring which can contain 1 or 2 nitrogen atoms and can be mono- or disubstituted by (C_1-C_6) -alkyl or doubly bonded oxygen or sulfur;

B is a bivalent radical from the group consisting of (C_1-C_6) -alkylene, (C_2-C_6) -alkenylene, phenylene, phenylene- (C_1-C_6) -alkyl, (C_1-C_6) -alkylenephenoxy, where the bivalent (C_1-C_6) -alkylene radical can be unsubstituted or substituted by a radical from the group consisting of (C_1-C_6) -alkyl, (C_2-C_8) -alkenyl, (C_2-C_8) -alkynyl, (C_3-C_{10}) -cycloalkyl, (C_3-C_{10}) -cycloalkyl- (C_1-C_6) -alkyl, optionally substituted (C_6-C_{14}) -aryl, (C_6-C_{14}) -aryl- (C_1-C_6) -alkyl optionally substituted in the aryl radical, optionally substituted heteroaryl and heteroaryl- (C_1-C_6) -alkyl optionally substituted in the heteroaryl radical;

D is $C(R^2)(R^3)$, $N(R^3)$ or $CH=C(R^3)$;E is $R^{10}CO$;R is hydrogen, (C_1-C_6) -alkyl, (C_3-C_8) -cycloalkyl, optionally substituted (C_6-C_{14}) -aryl or (C_6-C_{14}) -aryl- (C_1-C_6) -alkyl optionally substituted in the aryl radical;R⁰ is hydrogen, (C_1-C_6) -alkyl, (C_3-C_{12}) -cycloalkyl, (C_3-C_{12}) -cycloalkyl- (C_1-C_6) -alkyl, (C_6-C_{12}) -bicycloalkyl, (C_6-C_{12}) -bicycloalkyl- (C_1-C_6) -alkyl, (C_6-C_{12}) -tricycloalkyl, (C_6-C_{12}) -tricycloalkyl- (C_1-C_6) -alkyl, optionally substituted (C_6-C_{14}) -aryl, (C_6-C_{14}) -aryl- (C_1-C_6) -alkyl optionally substituted in the aryl radical, optionally substituted heteroaryl, heteroaryl- $(C_1-$

C_8 -alkyl optionally substituted in the heteroaryl radical, CHO, (C_1-C_8) -alkyl-CO, (C_3-C_{12}) -cycloalkyl-CO, (C_3-C_{12}) -cycloalkyl- (C_1-C_8) -alkyl-CO, (C_5-C_{12}) -bicycloalkyl-CO, (C_6-C_{12}) -bicycloalkyl- (C_1-C_8) -alkyl-CO, (C_6-C_{12}) -tricycloalkyl-CO, (C_6-C_{12}) -tricycloalkyl- (C_1-C_8) -alkyl-CO, optionally substituted (C_6-C_{14}) -aryl-CO, (C_6-C_{14}) -aryl- (C_1-C_8) -alkyl-CO optionally substituted in the aryl radical, optionally substituted heteroaryl-CO, heteroaryl- (C_1-C_8) -alkyl-CO optionally substituted in the heteroaryl radical, (C_1-C_8) -alkyl-S(O)_n, (C_1-C_{12}) -cycloalkyl-S(O)_n, (C_3-C_{12}) -cycloalkyl- (C_1-C_8) -alkyl-S(O)_n, (C_6-C_{12}) -bicycloalkyl-S(O)_n, (C_6-C_{12}) -bicycloalkyl- (C_1-C_8) -alkyl-S(O)_n, (C_6-C_{12}) -tricycloalkyl-S(O)_n, (C_6-C_{12}) -tricycloalkyl- (C_1-C_8) -alkyl-S(O)_n, optionally substituted (C_6-C_{14}) -aryl-S(O)_n, (C_6-C_{14}) -aryl- (C_1-C_8) -alkyl-S(O)_n, optionally substituted in the aryl radical, optionally substituted heteroaryl-S(O)_n or heteroaryl- (C_1-C_8) -alkyl-S(O)_n, optionally substituted in the heteroaryl radical, where n is 1 or 2;

R^1 is $X-NH-C(=NH)-(CH_2)_p$ or $\Sigma^1-NH-(CH_2)_p$, where p is 0, 1, 2 or 3;

X is hydrogen, (C_1-C_6) -alkyl, (C_1-C_6) -alkylcarbonyl, (C_1-C_6) -alkoxycarbonyl, (C_1-C_{18}) -alkylcarbonyloxy- (C_1-C_6) -alkoxycarbonyl, optionally substituted (C_6-C_{14}) -arylcarbonyl, optionally substituted (C_6-C_{14}) -aryloxycarbonyl, (C_6-C_{14}) -aryl- (C_1-C_6) -alkoxycarbonyl which can also be substituted in the aryl radical, $(R^8O)_2P(O)$, cyano, hydroxyl, (C_1-C_6) -alkoxy, (C_6-C_{14}) -aryl- (C_1-C_6) -alkoxy which can also be substituted in the aryl radical, or amino;

X^1 has one of the meanings of X or is $R^1-NH-C(=N-R'')$, where R' and R'' independently of one another have the meanings of X ;

R^2 is hydrogen, (C_1-C_8) -alkyl, optionally substituted (C_6-C_{14}) -aryl, (C_6-C_{14}) -aryl- (C_1-C_8) -alkyl optionally substituted in the aryl radical or (C_1-C_8) -cycloalkyl;

R^3 is hydrogen, (C_1-C_8) -alkyl, optionally substituted (C_6-C_{14}) -aryl, (C_6-C_{14}) -aryl- (C_1-C_8) -alkyl optionally substituted in the aryl radical, (C_1-C_8) -cycloalkyl, (C_2-C_8) -alkenyl, (C_2-C_8) -alkynyl, (C_2-C_8) -alkenylcarbonyl, (C_2-C_8) -alkynylcarbonyl, pyridyl, $R^{11}NH$, R^4CO , $COOR^4$, $CON(CH_3)R^{14}$, $CONHR^{14}$, $CSNHR^{14}$, $COOR^{15}$, $CON(CH_3)R^{15}$ or $CONHR^{15}$;

R^4 is hydrogen or (C_1-C_{28}) -alkyl which can optionally be mono- or polysubstituted by identical or different radicals R^4 ; R^4 is hydroxyl, hydroxycarbonyl, aminocarbonyl, mono- or di- $((C_1-C_{18})$ -alkyl)aminocarbonyl, amino- (C_2-C_{18}) -alkylaminocarbonyl, amino- (C_1-C_3) -

Serial No. 08/971,960

alkylphenyl-(C₁-C₄)-alkylaminocarbonyl, (C₁-C₁₈)-alkylcarbonylamino-(C₁-C₃)-alkylphenyl-
(C₁-C₂)-alkylaminocarbonyl, (C₁-C₁₈)-alkylcarbonylamino-(C₂-C₁₈)-alkylaminocarbonyl,
(C₆-C₁₄)-aryl-(C₁-C₃)-alkoxycarbonyl which can also be substituted in the aryl radical,
amino, mercapto, (C₁-C₁₈)-alkoxy, (C₁-C₁₈)-alkoxycarbonyl, optionally substituted
(C₃-C₈)-cycloalkyl, halogen, nitro, trifluoromethyl or the radical R⁵:

R⁵ is optionally substituted (C₆-C₁₄)-aryl, (C₆-C₁₄)-aryl-(C₁-C₃)-alkyl optionally substituted in
the aryl radical, a mono- or bicyclic 5- to 12-membered heterocyclic ring which can be
aromatic, partially hydrogenated or completely hydrogenated and which can contain one,
two or three identical or different heteroatoms from the group consisting of nitrogen,
oxygen and sulfur, a radical R⁵ or a radical R⁶CO-, where the aryl radical and,
independently thereof, the heterocyclic radical can be mono- or polysubstituted by identical
or different radicals from the group consisting of (C₁-C₁₈)-alkyl, (C₁-C₁₈)-alkoxy, halogen,
nitro, amino and trifluoromethyl:

R⁶ is R⁷R⁸N, R⁷O or R⁷S or an amino acid side chain, a natural or unnatural amino acid, imino
acid, optionally N-(C₁-C₈)-alkylated or N-((C₆-C₁₄)-aryl-(C₁-C₃)-alkylated)azaamino acid or
a dipeptide radical which can also be substituted in the aryl radical and/or in which the
peptide bond can be reduced to -NH-CH₂- and their esters and amides, where hydrogen or
hydroxymethyl can optionally stand in place of free functional groups and/or where free
functional groups can be protected by protective groups customary in peptide chemistry:

R⁷ is hydrogen, (C₁-C₁₈)-alkyl, (C₆-C₁₄)-aryl-(C₁-C₃)-alkyl, (C₁-C₁₈)-alkylcarbonyl, (C₁-C₁₈)-
alkoxycarbonyl, (C₆-C₁₄)-arylcarbonyl, (C₆-C₁₄)-aryl-(C₁-C₃)-alkylcarbonyl or (C₆-C₁₄)-aryl-
(C₁-C₁₈)-alkyloxycarbonyl, where the alkyl groups can optionally be substituted by an
amino group and/or where the aryl radicals can be mono- or polysubstituted, preferably
monosubstituted, by identical or different radicals from the group consisting of (C₁-C₃)-
alkyl, (C₁-C₃)-alkoxy, halogen, nitro, amino and trifluoromethyl, or is a natural or
unnatural amino acid, imino acid, optionally N-(C₁-C₈)-alkylated or N-((C₆-C₁₄)-aryl-(C₁-
C₃)-alkylated)azaamino acid or a dipeptide radical which can also be substituted in the aryl
radical and/or in which the peptide bond can be reduced to -NH-CH₂-;

R⁸ is hydrogen, (C₁-C₁₈)-alkyl, optionally substituted (C₆-C₁₄)-aryl or (C₆-C₁₄)-aryl-(C₁-C₃)-
alkyl which can also be substituted in the aryl radical:

Serial No. 08/971,960

R⁹ is hydrogen, aminocarbonyl, (C₁-C₁₈)-alkylaminocarbonyl,

(C₃-C₈)-cycloalkylaminocarbonyl, optionally substituted (C₆-C₁₄)-arylamino carbonyl, (C₁-C₁₈)-alkyl, optionally substituted (C₆-C₁₄)-aryl or (C₃-C₈)-cycloalkyl;

R¹⁰ is hydroxyl, (C₁-C₁₈)-alkoxy, (C₆-C₁₄)-aryl-(C₁-C₈)-alkoxy which can also be substituted in the aryl radical, optionally substituted (C₆-C₁₄)-aryloxy, amino or mono- or di-((C₁-C₁₈)-alkyl)amino;

R¹¹ is hydrogen, (C₁-C₁₈)-alkyl, R¹²CO, optionally substituted (C₆-C₁₄)-aryl-S(O)₂, (C₁-C₁₈)-alkyl-S(O)₂, (C₆-C₁₄)-aryl-(C₁-C₈)-alkyl optionally substituted in the aryl radical or R⁹NHS(O)₂;

R¹² is hydrogen, (C₁-C₁₈)-alkyl, (C₂-C₈)-alkenyl, (C₂-C₈)-alkynyl, optionally substituted (C₆-C₁₄)-aryl, (C₁-C₁₈)-alkoxy, (C₆-C₁₄)-aryl-(C₁-C₈)-alkoxy which can also be substituted in the aryl radical, optionally substituted (C₆-C₁₄)-aryloxy, amino or mono- or di-((C₁-C₁₈)-alkyl)amino;

R¹³ is hydrogen, (C₁-C₆)-alkyl, (C₆-C₁₄)-aryl-(C₁-C₈)-alkyl optionally substituted in the aryl radical or (C₃-C₈)-cycloalkyl;

R¹⁴ is hydrogen or (C₁-C₂₂)-alkyl which can optionally be mono- or polysubstituted by identical or different radicals from the group consisting of hydroxyl, hydroxycarbonyl, aminocarbonyl, mono- or di-((C₁-C₁₈)-alkyl)-aminocarbonyl, amino-(C₂-C₁₈)-alkylaminocarbonyl, amino-(C₁-C₂)-alkylphenyl-(C₁-C₈)-alkylaminocarbonyl, (C₁-C₁₈)-alkylcarbonylamino-(C₁-C₂)-alkylphenyl-(C₁-C₈)-alkylaminocarbonyl, (C₁-C₁₈)-alkylcarbonyl-amino-(C₂-C₁₈)-alkylaminocarbonyl, (C₆-C₁₄)-aryl-(C₁-C₈)-alkoxycarbonyl which can also be substituted in the aryl radical, amino, mercapto, (C₁-C₁₈)-alkoxy, (C₁-C₁₈)-alkoxycarbonyl, optionally substituted (C₂-C₈)-cycloalkyl, HOS(O)₂-(C₁-C₈)-alkyl, R⁹NHS(O)₂-(C₁-C₈)-alkyl, (R¹⁰O)₂P(O)-(C₁-C₈)-alkyl, tetrazolyl-(C₁-C₈)-alkyl, halogen, nitro, trifluoromethyl and R⁵.

R¹⁵ is R¹⁶-(C₁-C₆)-alkyl or R¹⁶:

R¹⁶ is a 6- to 24-membered bicyclic or tricyclic radical which is saturated or partially unsaturated and which can also contain one to four identical or different heteroatoms from the group consisting of nitrogen, oxygen and sulfur and which can also be substituted by

Serial No. 08/971,960

one or more identical or different substituents from the group consisting of (C₁-C₄)-alkyl and oxo;

b, c, and d are 1;

e is 0, 1, 2, 3, 4, 5 or 6;

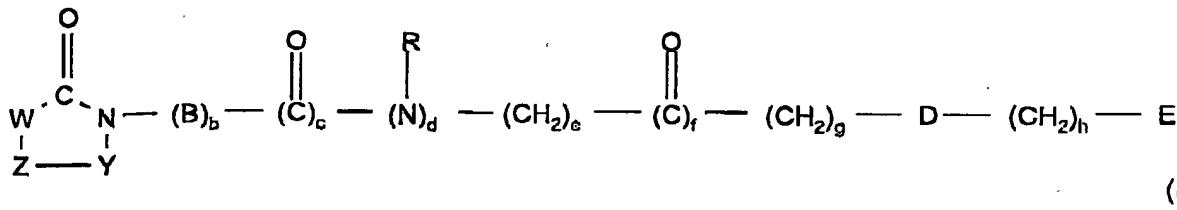
f is 0;

g is 0, 1, 2, 3, 4, 5 or 6;

h is 0, 1, 2, 3, 4, 5 or 6;

in all their stereoisomeric forms and mixtures thereof in any ratio, and of their physiologically tolerable salts.

22. (amended) A method for antagonizing VLA-4 comprising administering to a subject in need thereof an effective amount of [the preparation as claimed in claim 1] a preparation comprising an effective amount of at least one compound of the formula I:



in which

W is R¹-A-C(R¹³)<;

Y is a carbonyl;

Z is N(R⁶);

A is a bivalent radical from the group consisting of (C₁-C₆)-alkylene, (C₁-C₇)-cycloalkylene, phenylene, phenylene-(C₁-C₆)-alkyl, (C₁-C₆)-alkylenephenoxy, phenylene-(C₂-C₆)-alkenyl or a bivalent radical of a 5- or 6-membered saturated or unsaturated ring which can contain 1 or 2 nitrogen atoms and can be mono- or disubstituted by (C₁-C₆)-alkyl or doubly bonded oxygen or sulfur;

B is a bivalent radical from the group consisting of (C₁-C₆)-alkylene, (C₂-C₆)-alkenylene, phenylene, phenylene-(C₁-C₃)-alkyl, (C₁-C₃)-alkylenephenoxy, where the bivalent (C₁-C₃)-alkylene radical can be unsubstituted or substituted by a radical from the group consisting